

ORIGINAL ARTICLE

Single-center retrospective analysis of 162 cases with thymoma complicating myasthenia gravis

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Summary

Purpose: We conducted this study to retrospectively analyze the clinical effects of surgical resection for patients with myasthenia gravis (MG) complicated with thymoma.

Methods: 162 patients with myasthenia gravis complicated with thymoma, that were admitted to our hospital and underwent surgical disease resection from Nov. 1993 to Nov. 2015, were selected for this study. Analyzed were the pathology (2004 WHO), Masaoka clinical stage, myasthenia gravis types (Osserman types), myasthenic crisis during the perioperative period, and the relationship between recurrence and survival rates during follow-up visits. Operational methods included thymusectomy by sternal incision or video-assisted thoracoscopic thymusectomy.

Results: There were significant differences regarding distribution of clinical stages among different types of patholo-

gy. The operation time, efficacy rate, 5 and 10-year survival rates and complication rates during the perioperative period of video-assisted thoracoscopy were compared to those of the conventional surgery group. Among these groups, hemorrhage during operation, postoperative drainage and recurrence rate were significantly lower in the thoracoscopy group than in those of the conventional surgery group ($p < 0.05$).

Conclusion: The pathology type and clinical stages of thymoma complicating myasthenia gravis are related to the types of myasthenia gravis and the myasthenic crisis during perioperative period. Therefore, our results indicate that the thoracoscope treatment is safe and effective.

Key words: clinical stages, myasthenia gravis, myasthenic crisis, pathological types, thoracoscope, thymoma

Introduction

Thymoma is the most common tumor of the superior mediastinum, consisting of thymic epithelial cells and lymphocytes. It is characterized by low morbidity, low potential malignancy, and slow development [1]. The clinical symptoms are not typical as the main symptoms result from the pressure of thymus against adjacent tissues, which can lead to hoarseness, dyspnea, dysphagia, cough, chest pain, superior vein cava syndrome, spinal cord compression and others [2]. Of the patients, 35-45% can also present with complications of paraneoplastic syndromes, and MG, the latter being more common [3]. Thymoma with secondary MG does not have a valid drug treatment, and

therefore, surgical resection is adopted in these cases. The symptoms of 80% of the patients can be alleviated after operation, for which extended thymectomy is advocated [4]. There are few studies that have been conducted on thymoma biological characteristics and surgical treatment results. This study is an analysis of 162 surgical patients and the results are reported below.

Methods

Sample selection

Selected were patients that were admitted to our hospital, diagnosed with MG complicated with thymo-

ma and having undergone surgical resection between Nov. 1993 and Nov. 2015. This cohort included 78 males and 84 females aged 13-80 years (median 43). The majority of cases (n:102) presented with the clinical manifestations of blepharoptosis, diplopia, or weakness of limbs, weakness in chewing, dysphagia, dysarthria and dysphagia-dysarthria-dyspnea, 41 presented with chest distress, difficulty in breathing, coughing and hemoptysis, 15 cases presented with a mediastinal mass with diarrhea-irritable bowel syndrome and hyperthyroidism and 4 cases with superior vena cava obstruction syndrome.

Operational methods

Firstly, after anesthesia, pyridostigmine bromide and prednisone for the treatment of MG were applied. A small dose of pyridostigmine bromide (60mg/q8h) was combined with a plasmapheresis comprehensive therapeutic regimen. The operation was performed after the myasthenia symptoms were alleviated. The surgical method conducted was thymusectomy, with 84 (51.9%) patients having central whole sternum incision, 23 (14.2%) having upper segment incision of the sternum, and 55 (34.0%) having thymusectomy by video-assisted thoracoscopy. Eight patients were subjected to cervical collar incision thyroidectomy. Excision of the brachiocephalic vein, superior vena cava, partial lung and pericardium were conducted, followed by replacement with bovine pericardium artificial blood vessels and Gotax artificial blood vessels.

Observation indexes

Analyzed were the relationship among the different pathological types of MG, Masaoka clinical stages, MG types (Osserman types) and myasthenic crisis during the perioperative period. In 2004, WHO divided the classification of MG into Types A, B1, B2, B3, AB and C. In Type A, the the main cellular constituent is fusiform or oval thymus epithelial cell. In Type B1, the tissue is similar to normal thymus tissue with a common thymic corpuscle. In addition, the neoplastic epithelial cell has an oval shape, which helps distribute a large number of lymphocytes. In Type B2, the main cellular component is the neoplastic thymus epithelial cell, which allows the tumor cell to intersperse among the tissues full of lymphocytes, and a gap can be seen outside blood vessels. In Type B3, the tumor shows infiltrative growth, is short of complete envelope, and a polygon or a round epithelial cell is the main cellular element. Type AB is composed of Type A and Type B thymoma, which comprises lymphocytes. Type C consists of malignant cell morphological feature with existing mature lymphocytes and lack of immature lymphocytes.

The Masaoka clinical stages are as follows: Stage I refers to a complete envelope under light microscope without tumor cell invasion, Stage IIa is visible tumor

cell invasion under light microscope, stage IIb is tumor cell invasion of the surrounding pleura or adipose tissue, stage III is tumor cell invasion to adjacent organs, such as lung, pericardium and great vessels, and stage IV is tumor metastasis. The Osserman types include Type I,IIa, IIb, III and IV. Type I refers to symptoms from musculus ocularis, Type IIa includes mild weakness of the whole body without influencing respiratory muscles, and appropriate anticholinesterase reaction. Type IIb is significant face ptosis, diplopia, dyslalia, dysphagia and weak cervical muscles and limbs, with good body and limbs muscle, insensitivity of anticholinesterase and easy occurrence of myasthenia. Type III is sudden onset, typically within 6 months, of quick evolution of respiratory muscles involvement in the early stage, limbs muscles and body muscle involvement as well as low response to anticholinesterase. In this case, myasthenia crisis may easily occur and is characterized by high death rate and thymoma. Type IV is late onset morbus asthenicus with significant myasthenia, mostly accompanied with thymoma.

The clinical effects of different surgical methods include operation time, hemorrhage during operation, postoperative drainage, perioperative complications, recurrence rate and survival rate during the follow-up visit.

Statistics

SPSS20.0 software was used for statistical analysis. Measurement data was presented by mean \pm standard deviation, and t-test or one way ANOVA analysis were applied to compare differences between groups. Enumeration data was expressed as numbers or percents and comparison between groups utilized the χ^2 test. $P < 0.05$ indicated statistically significant difference.

Results

Relation between pathological types, Masaoka clinical stages and MG types

Among the 162 patients, there were 33 cases (20.4%) of Type A, 28 (17.3%) of Type B1, 30 (18.5%) of Type B2, 26 of Type B3 (16.0%), 42 (25.9%) of Type AB and 3 cases (1.9%) of Type C. The average maximum diameter of the tumors was 1.3 ± 0.5 cm, and the comparison of maximum diameter among patients of different pathology types revealed no significant differences ($p > 0.05$). With regards to clinical stages, there were 43 cases (26.5%) of stage I, 34 (21.0%) of stage IIa, 38 (23.5%) of stage IIb, 45 (27.8%) of stage III and 2 cases (1.2%) of stage IV. For MG types, there were 6 cases (3.7%) of Type I, 14 (8.6%) of Type IIa, 46 (28.4%) of Type IIb, 58 (35.8%) of Type III and 38 cases (23.5%) of Type IV.

Patients of Types I and IIa were graded mainly as Type A, patients of Type IIb and III were graded mainly as Type B, and patients of Type IV were graded as Type AB; differences were statistically significant ($p < 0.05$). The clinical stage of Type I, Type IIa and Type IV were stage II-IV mainly and the clinical stage of Type IIb and Type III were stage I-II mainly; differences were statistically significant ($p < 0.05$) (Table 1).

Relation between pathological types & Masaok clinical stages and myasthenic crisis during perioperative period

During the perioperative period, 3 patients (1.9%) died, among whom 1 case was a sudden death, and 2 cases died due to respiratory failure. Twenty-four patients (14.8%) underwent myasthenic crisis, and 6 cases (3.7%) were subjected to tracheotomy. There were 20 patients (83.3%) with Type IIb and Type III with myasthenic crisis in

MG types. There were 2 cases of Type I and Type IIa and 2 cases of Type IV. Eighteen cases (75.0%) had Type B, 4 cases of Type AB, and 2 cases Type A. In clinical stages, there were 16 cases (66.7%) of stage II, 5 cases of stage I and 3 cases of stage III and stage IV.

Clinical effect analysis of different operation methods

The postoperative follow-up time ranged between 5 months to 20.8 years, with a median time of 12.6 years. With regards to the remission rate of MG post-operation, the effective treatment rate was 85.5%. Twenty-four cases (15.1%) relapsed with tumor metastasis, 6 cases presented with simple thoracic implantation, 2 cases presented with thoracic implantation combined with contralateral lung squamous cell carcinoma, 5 cases presented with thoracic implantation combined with ipsilateral multiple pulmonary metastasis, 3 cases presented with simple pulmonary metastasis, 4

Table 1. Relation between pathological types & Masaok clinical stages and MG types, cases (%)

MG Types	Cases	Pathological types			Clinical Stage		Stages
		A	AB	B and C	I	II	III and IV
Type I and Type, Type IIa, n (%)	20	18 (90.0)	1	1	4	8 (40.0)	8 (40.0)
Type IIb	46	6	11 (23.9)	29 (63.0)	16 (34.8)	22 (47.8)	8
Type III	58	4	9 (15.5)	45 (77.6)	22 (37.9)	26 (44.8)	10
Type IV	38	5	24 (63.2)	9 (23.7)	1	16 (42.1)	21 (55.3)

Table 2. Clinical effect analysis of different operation methods

Groups	Cases	Operation time (min)	Hemorrhage during operation (ml)	Postoperative drainage (ml)	Effective rate n (%)	Reccurrence rate n (%)	5-year survival rate (%)	10-year survival rate (%)
Thoracoscope group	55	134.6±23.6	145.7±35.4	245.8±46.8	46(83.6)	5(9.1)	52(94.5)	49(89.1)
Conventional operation group	107	125.7±24.5	326.5±56.7	465.9±67.9	92(86.0)	23(21.5)	103(96.3)	99(92.5)
t/x ²		0.125	5.237	5.436	0.158	3.910	0.010	0.195
P		0.869	0.036	0.032	0.691	0.048	0.920	0.659

Table 3. Comparison of perioperative complications by different operation methods, n (%)

Groups	Cases	Death	Myasthenia crisis	Infection	Pleural effusion	Nerve, blood vessel and muscle injury	Incidence of complications
Thoracoscopic group	55	1	9	1	2	1	14 (25.5)
Conventional operation group	107	2	15	2	5	4	28 (26.2)
x ²							0.010
P							0.922

cases presented with tumor recurrence in the mediastinum, lung, superior vena cava and 4 cases presented with thoracic vertebra, rib, and hepatic metastasis. The survival rate was 95.6% in 5 years and 92.3% in 10 years. The operation time, effective rate, 5- and 10-year survival rate and complication occurrence rate during the perioperative period of the thoracoscopic group were compared to those of the conventional surgery group. Hemorrhage during operation, postoperative drainage and recurrence rate were significantly lower than in those of the conventional surgery group ($p < 0.05$) (Tables 2 and 3).

Discussion

Relation between thymoma biological characteristics and MG

MG is an acquired autoimmune disease that leads to activation of B-lymphocytes as well as neuromuscular junction subsynaptic membrane acetylcholine receptors (AChR) antibody-mediated action. In addition, MG is also characterized by inability of extraocular muscles, visceral smooth muscles and skeletal muscles of the whole body. The thymus plays a role in the occurrence of MG and in fact, an anti-AChR antibody can be found within thymoma, hyperplastic thymus and superior mediastinum adipose tissue [5]. Thymus excision can eliminate the production of MG initial autoimmune response factor and reduce the production of AChR antibody [6]. According to a study [7], type B thymoma can easily complicate MG. Therefore, the higher the Masaoka clinical stage, the easier it is for a complication to develop, which may cause a postoperative myasthenia crisis to occur easily. Another study [8] also suggests that the lower the Masaoka clinical stage, the easier it is for a postoperative myasthenia crisis to occur.

The results of this study found that the pathology of Type I and Type IIa in MG types were mainly Type A, the pathology of Type IIb and Type III were mainly Type B, and the pathology of Type IV were Type AB mainly. The clinical stage of Type I, Type IIa and Type IV were mainly stage II-IV and the clinical stage of Type IIb and Type III were stage I-II mainly. Myasthenia crisis occurs in Type IIb and Type III in MG types, Type B in pathology and stage II in clinical stages. In addition, the MG symptoms of Type B thymoma is more severe, and is associated with higher homeocyte-mediated AChR antibody production [9]. The MG symptoms of early clinical

stages are serious, which is supposed to relate to a complete thymus mediated autoimmune function [10]. Type B thymoma and early clinical stages excision can easily lead to myasthenia crisis due to the rapid reduction of AChR antibody.

Relation between thymoma biological characteristics and survival prognosis

Our results show that thymoma grows slowly and a patient can survive for an extended period of time without any symptoms but sluggishness [11]. The postoperative tumor metastasis rate is approximately 15.1%, and the survival rate is 95.6% for 5 years and 92.3% for 10 years. Thymoma metastasis and death mostly occurs in patients with Type B2 or higher and Masaoka Stage IIb. Metastasis occurs in thoracic implantation lung, bone and liver, suggesting that the upper the pathology types and stages, the poorer the prognosis [12].

During the operation, it was noticed that anatomic structures adjacent to thymoma were infiltrated and included brachiocephalic vein, superior vena cava, pericardium, phrenic nerve and lung. The pleura and pericardium dissemination before the operation was difficult to identify. Some thymomas can easily invade the pleura, pericardium, great vessels, and even the heart. For invasion and tumor metastasis of the heart and great vessels, the stage should be set to IV, however, it should be classified in conjunction with the criteria of the Masaoka three clinical stages. Therefore, the clinical stage criteria need to be further defined. For thymoma the whole thymus and the surrounding fat should be resected [13]. On the one hand, thymoma has the potential for malignancy, and hence, a whole thymus excision meets the tumor-free principle. However, on the other hand, it also conforms to the MG treatment principle. The operation results were equivalent when the whole sternum was opened, the upper segment of the sternum was cut and thoracoscopic thymus operation was performed. The operation time, efficacy rate, 5- and 10-year survival rate and the complication rates during the perioperative period of the thoracoscopic approach were compared. The incidence of hemorrhage during operation, postoperative drainage and recurrence rates in patients that underwent thoracoscopic surgery was significantly reduced, with little trauma and quick recovery. According to thoracic implantation and lung metastatic tumor, it was found that a chest wash was necessary, which could clear the vestigial tumor tissue.

In order to treat patients with severe MG, a small dose of pyridostigmine bromide combined with plasmapheresis comprehensive therapeutic regimen is applied at our hospital. The aim of treating with pyridostigmine bromide, which is a cholinesterase inhibitor, is to alleviate symptoms and reduce the cholinergic effects [15]. As cholinesterase inhibitors can increase glandular secretion, spittle and respiratory tract secretion, critical MG manifests as a weak cough and dysphagia, which can lead to airway obstruction. Plasmapheresis can relieve the symptoms quickly by a

non-selective separation of the plasma in order to eliminate the antibody, mediation of immunoreaction, and immune complex in plasma [16].

In conclusion, the pathological type and clinical stage of thymoma complicated with MG is related to MG types and myasthenic crisis during the perioperative period. In addition, the thoracoscopic treatment is safe and effective.

Conflict of interests

The authors declare no conflict of interests.

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